

Can the novel inflammatory markers be used in the prediction of Gestational Diabetes Mellitus or to strengthen the screening test?

Use of novel inflammatory markers for GDM prediction

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Abstract

Aim: The pathophysiology of Gestational diabetes mellitus (GDM) has not been exposed properly, however, some clues designate the systematic inflammation. New inflammatory markers such as mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and platelet distribution width (PDW) might play a crucial role in predicting or diagnosing GDM.

In this study, we aimed to evaluate the possible association between the CBC parameters (MPV, PDW, NLR, PLR values) which were sampled on the test day of the glucose challenge test and GDM.

Material and Methods: Pregnant women who underwent 50 gr GCT were evaluated. Among them, patients with an abnormal 100 g oral glucose tolerance test (OGTT), and normal OGTT results were recruited in groups 1 and 2, respectively. Women with normal GCT were included in Group 3 as controls. Patients who had complete hemogram count on the day of GCT or OGTT were reviewed. The MPV, NLR, PLR and PDW parameters were analyzed statistically between groups.

Results: A total of 9819 patients were screened with 50gr GCT over a 3-year period. The distribution of patient numbers within the groups in groups 1, 2, and 3 was 167, 400, and 610 patients, respectively. There was no statistically significant difference between Group 1 and Group 2 for NLR, PLR, Platelet, MPV, PDW, neutrophil, lymphocyte, and hemoglobin ($p > 0.05$). Healthy patients had higher MPV and lower PDW values than patients with GDM, which differed significantly.

Discussion: Neither the novel inflammatory markers PLR, and NLR, nor the platelet parameters PDW, and MPV seemed to be beneficial to predict GDM or strengthen the 50g glucose challenge test during the routine screening period. These markers might be related with chronic circumstances, and the usefulness of novel inflammatory markers might be revealed in the near future.

Keywords

Inflammation marker; Neutrophil-to-lymphocyte ratio; Mean platelet volume; Gestational diabetes mellitus; Platelet-to-lymphocyte ratio; Platelet distribution width

DOI: 10.4328/ACAM.20362 Received: 2020-10-04 Accepted: 2020-11-03 Published Online: 2020-11-15 Printed: 2021-06-01 Ann Clin Anal Med 2021;12(6):621-625

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Introduction

Gestational diabetes mellitus (GDM) is carbohydrate intolerance resulting in hyperglycemia which is primarily diagnosed during pregnancy. Physiological changes in pregnancy induce peripheral resistance to insulin to ensure a sustained supply of glucose to the fetus resulting in a 250% increase in insulin production [1]. The circumstances that cannot respond to these changes would cause GDM. The pathophysiology of GDM has not been elucidated properly. Recent studies emphasize that systematic inflammation may play a key role in susceptibility to GDM [2, 3]. The factors that initiate the primary inflammation are controversial. The type of the inflammation, acute or chronic, in gestational mellitus is controversial. However, several serum markers were investigated to identify the responsible elements, so that prediction or prevention of DM or GDM could be possible. In recent years, physicians have intensified their attention on hemogram parameters for systemic inflammation. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are considered as novel markers of systemic inflammation [4, 5]. These parameters could be achieved using a complete blood count (CBC) test, which is inexpensive, feasible, and accessible. Other CBC parameters, which could give precious information about diabetes are mean platelet volume (MPV) and platelet distribution width (PDW) [6, 7]. Several studies have depicted that these parameters could be correlated with DM and GDM, especially with accompanying microvascular complications [8, 9]

There is no consensus regarding the optimal approach for screening gestational diabetes mellitus. One-step and two-step approaches were recommended and utilized for GDM screening and diagnosis. The American College of Obstetricians and Gynecologists (ACOG) continues to recommend a two-step approach using the Carpenter-Coustan criteria cutoffs [10]. In our hospital, all patients with low risk of GDM are screened using a two-step approach between the 24th and 28th weeks of gestation. If the patient has an increased risk factor for GDM, a 75gr glucose load challenge test is performed regardless of the gestation week. Consumption glucose for a gestational diabetes test can make patients feel like it could harm the baby or themselves, which may be most related to obtaining information from the media or from unreliable sources. Many patients may hesitate to undergo glucose load tests, especially for repeated intravenous blood samplings [11]. Several studies were conducted to evaluate the prediction or association between CBC parameters and GDM with few participants. We aimed to evaluate the possible association between CBC parameters (MPV, PDW, NLR, PLR values), which were sampled on the day of testing the glucose challenge test and GDM.

Material and Methods

A retrospective cohort study was designed after approval of the local ethics committee in Bursa Yuksek Ihtisas Training and Research Hospital, University of Health Sciences. Women who had a 50 g glucose challenge test (GCT) without starvation at 24 -28 weeks of gestation between June 2016 and September 2019, were reviewed. All women with plasma glucose values between 140 and 199 mg/dl after 1 hour following the 50 g glucose intake were advised to undergo a 3-hour 100-gram

oral glucose tolerance test (OGTT) after a 3-day standard diet, which was comprised of a daily intake of at least 250 g carbohydrates. Initially, a blood sample was obtained after 8-10 hours of fasting. After measuring fasting blood glucose, patients were instructed to take 100 g of glucose. Blood samples were repeated at one-hour intervals a total of three times. GDM diagnosis was established based on Carpenter-Coustan criteria after OGTT if two or more blood glucose values were higher than the defined cutoff values, namely, fasting blood glucose levels ≥ 95 mg/dL and blood glucose levels of ≥ 180 mg/dL, ≥ 155 mg/dL and ≥ 140 mg/dL during the first, second, and third hours, respectively [12]. Venous blood glucose levels were measured by the Cobas® e 602 modules (Roche, New Jersey, USA).

Patients who had a complete hemogram count (CBC) test on the day of GCT or OGTT were recruited into the study. Patients with a family history of DM, previous history of GDM, previous delivery of macrosomia, unexplained fetal loss, elevated risks of GDM including metabolic syndrome, polycystic ovary syndrome, use of corticosteroids, and patients with multiple pregnancies were excluded from the study because these patients underwent directly 75 gr or 100gr OGTT regardless of the gestational week in our hospital. Patients who had any concomitant disease that can affect complete blood count like anemia (Hb < 10.5 gr/dl), leukocytosis (white Blood Cell > 15.000 μ /ml), thrombocytopenia (Platelets < 150.000 μ /ml), auto-immune disease, chronic inflammatory disease or hematological disorders were also excluded.

All laboratory data and patient information were retrieved from Bursa Yuksek Ihtisas Training and Research Hospital database. All venous blood samples for CBC examination were collected in 2 mL EDTA tubes and analyzed using an automated hematology analyzer (Mindray BC-6800 Plus, Shenzhen, China) within 1 hour to avoid time-dependent ultrastructural morphological changes in platelets. In our laboratory, the normal range for MPV and is taken as 7,8–11 femtoliters (fl).

Patients were divided into three groups. Group 1 consisted of the patients diagnosed with GDM. The diagnosis was confirmed by two or more blood glucose values that were higher than the defined cutoff values in OGTT, which was performed after an abnormal GCT test (plasma glucose value between 140 and 199).

Group 2 consisted of patients with false positive GCT, which was defined as normal OGTT (all values were normal or only one value was higher than the cutoff values) after abnormal GCT (plasma glucose value was between 140 and 199).

Group 3 consisted of the patients with plasma glucose values < 140 mg/dl in GCT (healthy control group).

Complete blood count parameters (MPV, PDW, platelet, hemoglobin, NLR, PLR) which were sampled on the day of GCT or OGTT, were reviewed for each patient.

Primarily we aimed to investigate the difference between these groups in terms of CBS parameters to find out a proper threshold for GDM to prevent glucose-consuming tests.

The study sample size determination was calculated by evaluating similar studies with a statistical power analysis program. As a result, to achieve 80% power with 5% type 1 error to detect a minimum clinically significant difference, at

least 114 individuals must have been included in each group. Statistical analysis was performed using the SPSS 24.0 software for Windows. The normal distribution of continuous variables was evaluated using the Shapiro-Wilk test. Skewness and kurtosis values were also used to determine the normality of the population. Due to the normality results, patients' data were compared between three groups with a one-way ANOVA test. Levene's test was used to assess the homogeneity of the variances. An overall p-value of less than 0,05 was considered statistically significant.

Results

The total number of patients who were screened with 50g GCT between 24-28 weeks over a 3-year period was 9819. Among these, GCT test results of 1259 patients were between 140 and 199. The number of patients who underwent OGTT was 690. The rest of the patients either declined the diagnostic test or underwent the testing in another health center. One hundred ninety-six patients were diagnosed with GDM (Group 1) after OGTT. Twenty-nine patients were excluded from the study due to exclusion criteria (11 did not have a CBC test, 2 had twin pregnancy, 8 had anemia, 3 had leukocytosis and 5 had thrombocytopenia). Four hundred ninety-four patients had a normal diagnostic test with abnormal screening test (false positive GCT), and 400 of them were included in the study. Ninety-four patients were excluded (27 did not have CBC test, 7 had twin pregnancy, 36 had anemia, 9 had leukocytosis and 15 had thrombocytopenia) due to exclusion criteria. Six hundred and ten patients with normal screening tests were included in the study as a control group (Group 3).

Patients with GDM were older than the rest. Patients in Group 2 were also older than healthy controls. Evaluation CBC components revealed that there was no statistically significant difference between groups.

The novel inflammatory parameters such as NLR and PLR were higher in groups 1 and 2; however, these levels did not differ significantly. Mean platelet volume and the platelet distribution width were the only parameters that differed significantly in the present study. MPV was higher in healthy subjects than the false positive GCT groups and GDM groups, which differed significantly. Opposite of MPV, PDW was lower in healthy, and this difference was significant.

Laboratory results of the patients and comparison of the parameters with p-values were evaluated in Table 1.

The main determinants of gestational diabetes were evaluated via correlation analysis. It was revealed that age (as expected) and PDW positively, and MPV negatively correlated with GCT values; however, these correlations were weak (r<0.4). Correlation analysis of the parameters with age was evaluated. MPV, PDW, PLR were associated with age, yet this correlation was very weak (r<0.2). The correlation between parameters with GCT and age was evaluated in Tables 2 and 3.

Table 2. Evaluation of the correlation between the parameters with glucose challenge test results

	Glucose Challenge Test Results	
	r	p
Age	0.393	0.001
MPV	- 0.369	0.001
PDW	0.268	0.001
NLR	0.040	0.860
PLR	0.028	0.170

MPV: Mean Platelet Volume, PDW: Platelet Distribution Width NLR: Neutrophil- to- Lymphocyte ratio, PLR: Platelet- to- Lymphocyte Ratio

Table 3. Evaluation of the correlation between the parameters with glucose challenge test results

	Age	
	r	p
MPV	- 0.132	0.001
PDW	0.117	0.001
NLR	0.022	0,228
PLR	0.063	0.015

MPV: Mean Platelet Volume, PDW: Platelet Distribution Width NLR: Neutrophil- to- Lymphocyte ratio, PLR: Platelet- to- Lymphocyte Ratio

Table 1. Serum levels of markers (mean values and standard deviations) and comparison of them between groups

	Group 1 (GDM) n=167	Group 2 (False Positive GCT) n=400	P value Group 1 & 2	Group 3 (Healthy Controls) n=610	P value Group 1 & 3	P value Group 2 & 3
Age (years)	32,5 ± 5,7	29,9 ± 6	<0,001	26,5 ± 5,6	<0,001	<0,001
Platelet (µl/ml)	251 ± 61	246 ± 56	0,63	242 ± 52	0,14	0,43
Neutrophil (µl/ml)	7,4 ± 1,8	7,3 ± 2,3	0,22	7,7 ± 2	0,96	0,17
Lymphocyte (µl/ml)	1,89 ± 0,54	1,95 ± 0,69	0,54	1,92 ± 0,54	0,77	0,83
Hemoglobin (gr/dl)	11,5 ± 0,82	11,8 ± 0,81	0,78	11,5 ± 0,82	0,99	0,68
MPV (Femtoliters)	9,01 ± 1,2	8,9 ± 1,4	0,97	10,01 ± 1,05	<0,001	<0,001
PDW	16,5 ± 0,8	16,5 ± 0,7	0,76	16,1 ± 0,3	<0,001	<0,001
NLR	4,19 ± 1,5	4,25 ± 1,6	0,89	4,04±1,4	0,52	0,08
PLR	140 ± 42	134 ± 39	0,3	133±39	0,13	0,86

GDM: Gestational diabetes mellitus, GCT: Glucose challenge test, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, NLR: Neutrophil- to- Lymphocyte ratio, PLR: Platelet- to- Lymphocyte Ratio

Discussion

Gestational diabetes mellitus emerges due to the insufficient response with an adequate amount of insulin secretion to physiological changes during pregnancy. The prevalence of the disease bears an increasing trend due to the increasing risk factors. Causes of insulin resistance such as obesity, polycystic ovary syndrome, genetic history of diabetes, advanced age, and steroid consumption are major risk factors of GDM. Placental growth hormone, corticotropin-releasing hormone, placental lactogen, tumor necrosis factor- α (TNF- α), and progesterone initiate an adequate metabolic environment for the necessity of the fetus. The effect of these hormones arises apparently during the late second trimester of the pregnancy. Thus, almost all the obstetrician associations recommend performing GDM screening tests during 24-28 weeks of gestation.

Recent studies declared the benefits of the GCT and OGTT without any harm to the fetus and pregnant women; however, some patients have a prejudice about the test. GCT could be a more reasonable option, and OGTT might be occasionally challenging for patients with blood testing done four times and high glucose levels. Every single day as the novel diagnostic tests evolve, patients request a test without any intervention. They require a test without consuming glucose or other molecules. We aimed to investigate whether CBC parameters could benefit to GDM diagnosis.

Our findings revealed that patients with GDM are significantly older than healthy participants, and this is consistent with the literature since age is the major risk factor for GDM. Patients with GDM were also significantly older than patients with false-positive GCT. There is no consensus on this data. When evaluating the number of participants and the including criteria of the studies, it was found that the present study included the largest number of participants compared to other studies in the literature [13-15], and this is the strength of our study. We also depicted that patients with false positive OGT were older than healthy controls. In this regard, increased age might affect the response of the pancreatic beta cells to acute glucose consumption.

Physiological changes in pregnancy have an impact on complete blood count parameters [16]. Leukocytosis with increased lymphocytes is normal. Any disease could affect the distribution of blood components. To diminish this effect, we excluded participants with anemia, leukocytosis, thrombocytopenia, or thrombocytosis [17]. The levels of the neutrophils, lymphocytes, and hemoglobin did not affect due to gestational diabetes status. Comparing the NLR and PLR which were determined as novel inflammatory markers, we found no statistically significant difference between all groups. The mean values of these parameters were higher in GDM and false positive patients than the healthy control group, with no statistically significant difference. Even though NLR and PLR are supposed to be inflammatory markers, there is no consensus as to whether they are indicative of acute or chronic inflammatory processes. Recently, NLR and PLR have represented a statistical significant difference in patients with chronic diseases with concomitant end organ failure [18-20]. Aktulay et al. declared a significantly increased NLR and PLR in patients with GDM although they included only 29 patients

in each group [21]. These markers have also been evaluated as predictors of GDM during the first trimester of pregnancy, yet the studies depicted no benefit on this subject [22, 23]. In the light of the studies, NLR and PLR may be beneficial in chronic situations. Thus, due to our findings, NLR and PLR were not beneficial for distinguishing patients with GDM. On the other hand, GDM seems to be an acute illness, which exposes itself in the late second trimester of the pregnancy. We do not think that this disease can be detected using chronic inflammation markers.

The other CBC markers, which were investigated in GDM and DM, were thrombocyte parameters (Platelet count, MPV, PDW). Authors have investigated MPV as a predictor for GDM or to follow up serum glucose regulation. One of the major aims of the present study was the use of MPV and PDW as a diagnostic tool for GDM with a study with broad participation. Due to the result of our study, no statistically significant difference has occurred comparing MPV, PDW, and platelet counts between GDM patients and false-positive GCT patients. Although the mean values in all groups were within the normal MPV range, the healthy controls had a higher mean level than the false positive GCT group and also GDM group. This result was contrary to many articles [23-25]. A meta-analysis declared that MPV values were significantly higher in GDM patients; however, authors also remarked the heterogeneity of the studies and a possible bias [6]. When comparing studies in the literature with our study, the interesting fact was that our study not only had one of the largest numbers of participants, but also had clear and strong inclusion and exclusion criteria. We have stated that using MPV values did not seem beneficial to diagnose or predict GDM at late second trimester of the pregnancy. Scanning tests were proposed to be performed between 24-28-week of gestation. During this period of the pregnancy, the maximum effect of the pregnancy diabetogenic hormones on metabolism was possible. Thus, in this period, the influence of diabetes on the CBC parameters might not be initiated.

PDW, which was another test for thrombocyte function, was also investigated as a marker for GDM. The difference was significantly higher in patients with abnormal GCT (GDM and false positive GCT) than healthy control conversely to MPV values. Comparing GDM patients and the false positive group, it was found that PDW was not a good marker for distinguishing GDM patients as well. There is still no consensus on the effect of GDM on MPV and PDW [24, 25]. More studies examining PDW in GDM are required for this issue.

A correlation analysis was calculated to find whether the parameters might be a good diagnostic tool. Age, MPV and PDW were correlated with GCT results, with weak or very weak correlation. Age was also analyzed particularly with the CBC parameters. The result was the same as a very weak correlation; however, the strengths of these correlations were also very weak.

In conclusion, neither the novel inflammatory markers PLR, and NLR nor the platelet parameters PDW, and MPV were beneficial to predict GDM or strengthen the 50g glucose challenge test during the routine screening period. These markers may be related to chronic circumstances.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Deniz Simsek, Yasin Altekin. Can the novel inflammatory markers be used in the prediction of Gestational Diabetes Mellitus or to strengthen the screening test? *Ann Clin Anal Med* 2021;12(6):621-625